UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,631	10/31/2006	Sonja Bromer	1131-15-PCT-PA-TD	9726

22145 7590 01/05/2011

KLEIN, O'NEILL & SINGH, LLP
18200 VON KARMAN AVENUE
SUITE 725
IRVINE, CA 92612

EXAMINER	
FRAZIER, BARBARA S	
ART UNIT	PAPER NUMBER
1611	
MAIL DATE	DELIVERY MODE
01/05/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,631	BROMER ET AL.	
	Examiner	Art Unit	
	BARBARA FRAZIER	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *1 and 8-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-7 and 12-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/3/10 has been entered.

Status of Claims

2. Claims 1-16 are pending in this application.

3. Claims 1 and 8-11 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6/16/10.

4. Claims 2-7 and 12-16 are examined.

Specification

5. The objection to the specification as failing to provide proper antecedent basis for the claimed subject matter in claim 7 is withdrawn in view of Applicant's amendment to claim 7.

Claim Rejections - 35 USC § 112

6. The rejection of claims 2, 5-7, and 12-16 under 35 U.S.C. 112, second paragraph is withdrawn in view of Applicant's amendments to claims 2-5 which clarifies the presence of both "at least one progestagens" and "at least one estrogen".

7. The rejection of claim 6 under 35 U.S.C. 112, second paragraph is withdrawn in view of Applicant's amendment to claim 6.

Claim Rejections - 35 USC § 103

8. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The rejection of claims 2-7 and 12-16 under 35 U.S.C. 103(a) as being unpatentable over Simon et al in view of Trotter et al has been modified as follows:

9. Claims 2-7 and 12-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simon et al (EP 391396, cited by Applicants) in view of Trotter et al (J. Clin. End. Metab. 84(12), 4531-4535, 1999, cited by Applicants) and/or Heckenmuller et al (US Patent 5,514,673).

The claimed invention is drawn to a hormone-containing isotonic oil emulsion for intravenous administration comprising at least one progestagens and at least one estrogen; an oil phase; an antioxidant; an emulsifier; and an aqueous phase; wherein the at least one progestagens and the at least one estrogen are dissolved in the oil phase prior to being mixed with the aqueous phase (see claim 2).

Simon et al teach medicinal oil-in-water emulsions comprising an effective amount of a lipophilic drug, MCT oil optionally in combination with vegetable oil, about 0.05-20% of phospholipid (emulsifier), about 0.03-10% of a non-ionic surfactant (co-emulsifier) and about 0.05-5% of an ionic surfactant (co-emulsifier) (abstract). The compositions may further comprise an antioxidant such as α-tocopherol (page 5, lines 1-2); compositions comprising α-tocopherol are exemplified (Examples 1 and 2). The compositions are suitable for parenteral administration (page 4, lines 9-10), including intravenous administration (page 5, lines 19-22). Suitable hydrophobic drugs include lipophilic steroids, such as progesterone (page 5, lines 3-8). The compositions may be prepared by preparing an oily solution comprising oily carrier and hydrophobic drug, and then mixing the oily solution with the aqueous solution (see page 5, lines 23-34).

While Simon et al teach that progesterone may be one of the lipophilic drugs employed in the emulsion, Simon et al do not specifically teach an emulsion containing progesterone and an estrogen.

Trotter et al teach an oil-in-water emulsion of an estradiol (an estrogen) and pregn-4-ene-3,20-dione (progesterone, a progestagen) in a phospholipid-stabilized soybean oil emulsion, administered as an IV infusion (see page 4532, 1st column). Trotter et al teach that administration of progesterone and estradiol in extremely preterm infants provides benefits including improved bone mineral accretion and less chronic lung disease (abstract and page 4535).

Heckenmuller et al teach a pharmaceutical composition having a form suitable for transmucosal administration containing progesterone and/or estradiol as an active

ingredient (abstract). In its background discussion, Heckenmuller et al teach that parenteral administration of the sex hormones is known, albeit with inconveniences (col. 1, lines 15-38). Heckenmuller et al teach that its formulation can be manufactured by conventional methods for preparing two-phase emulsion systems, whereby progesterone and/or estradiol are dissolved in the oil be used prior to admixing with the aqueous phase (col. 3, lines 5-11).

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to administer progesterone and estradiol in the oil-in-water emulsion of Simon et al; thus arriving at the claimed invention. One skilled in the art would be motivated to do so because the administration of progesterone and estradiol provides the benefits of improved bone mineral accretion and less chronic lung disease, as taught by Trotter et al. One would reasonably expect success from the administration of progesterone and estradiol in the oil-in-water emulsion of Simon et al because Simon et al fairly teach and suggest that lipophilic steroids, including progesterone, may be used in its emulsion, and because Trotter et al teach that progesterone and estradiol may be administered in phospholipid-stabilized oil-in-water emulsions.

Additionally or alternatively, it would have been obvious to a person having ordinary skill in the art at the time the invention was made to administer progesterone and estradiol in the oil-in-water emulsion of Simon et al by dissolving the hormones in the oil phase prior to being mixed with the aqueous phase; thus arriving at the claimed invention. One skilled in the art would be motivated to do so, with a reasonable

expectation of success, because dissolving said hormones in the oil phase prior to being mixed with the aqueous phase is a conventional method for preparing two-phase emulsion systems, which would include those formed for parenteral use, as taught by Heckenmuller et al. (It is noted that, while Heckenmuller et al teach that there are "inconveniences" associated with parenteral (e.g., intravenous) use, such as the need for sterile delivery devices and medical assistance, Heckenmuller et al also teach that parenteral administration does provide the benefit of circumventing the undesired first pass effect (from oral administration), and the "inconveniences" noted by Heckenmuller do not prevent its emulsion from being used for intravenous administration.)

Regarding claims 3 and 4, Trotter et al teach that the concentration of estradiol is between 2.2 ng/ml and 0.22 mg/ml, and the concentration of pregn-4-ene-3,20-dione is between 0.4 ug/ml and 1.25 mg/ml (page 4532, 1st column). These concentrations result in ratios of 6.25:1 (1.25 mg/ml to 0.22 mg/ml) and 181:1 (0.4 ug/ml to 2.2 ng/ml). These ratios are within Applicant's range of from 2:1 to 200:1.

Regarding claim 4, Trotter et al teach that the concentration of estradiol is between 2.2 ng/ml and 0.22 mg/ml (which is equivalent to 0.00000022 – 0.022% by weight), and the concentration of pregn-4-ene-3,20-dione is between 0.4 ug/ml and 1.25 mg/ml (which is equivalent to 0.00004 – 0.125% by weight (page 4532, 1st column). These amounts overlap those of the claimed invention; one skilled in the art would be motivated to manipulate the amounts of estradiol and progesterone within said ranges by routine experimentation, in order to optimize the efficacy of the resultant composition.

Additionally or alternatively regarding claims 3 and 4, Heckenmuller et al exemplify amounts of estradiol of 0.055 and 0.068%, and amounts of progesterone of 0.967 and 1.2% (Examples 3-6), which result in a ratio of approximately 18:1; these values are within Applicant's ranges taught in claims 3 and 4.

Regarding claim 5, Trotter et al teach that the active agents used are progesterone and estradiol (abstract and page 4532).

Regarding claim 6, Simon et al teach use of mid chain triglycerides (abstract) such as Miglyol 812 (C8-C10 triglycerides) (page 4, lines 30-31).

Regarding claim 7, Simon et al teach amounts of phospholipid of 0.05-20% (abstract). This range overlaps that of the claimed invention; one skilled in the art would be motivated to manipulate the amount of phospholipid from within said ranges by routine experimentation, in order to optimize the stability of the resultant composition.

Regarding claims 12 and 13, Simon et al teach amounts of non-ionic surfactant of 0.03-10% and ionic surfactant of 0.05-5% (abstract). These amounts overlap those of the claimed invention; one skilled in the art would be motivated to manipulate the amount of phospholipid from within said ranges by routine experimentation, in order to optimize the stability of the resultant composition.

Regarding claim 14, Simon et al teach that the compositions may further comprise an antioxidant such as α-tocopherol (page 5, lines 1-2).

Regarding claim 15, Simon et al exemplify amounts of α-tocopherol of 0.05% of the emulsion, and 20.55% of oil phase (Example 1). Therefore, the amount of α-tocopherol would be equivalent to 0.24% of the oil phase, or 240 mg based on 100 g of

the oil phase. This amount is within Applicant's range of 10mg to 1000mg based on 100g of the oil phase.

Regarding claim 16, Simon et al teach that the more preferred pH is 6.0-8.0, especially for parenteral administration (page 4, lines 28-29).

Response to Arguments

10. Applicant's arguments filed 11/3/10 have been fully considered but they are not persuasive.

Applicants first argue that Trotter teaches away from the claimed emulsion by teaching dissolving the hormones estradiol and progesterone in 98% ethanol before adding it to the oil phase, citing *In re Gurley*: "A reference is said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant" (page 8 of Applicant's Remarks).

This argument is not persuasive. While Trotter does teach adding estradiol and progesterone to ethanol prior to adding to the emulsion, there is nothing in the teaching of Trotter that would lead one skilled in the art to believe that the emulsion could not also be formed by adding the estradiol and progesterone to the oil phase prior to forming the emulsion, as taught by Simon and Heckenmuller. Furthermore, it is noted that the claims are drawn to the emulsion itself, not a process of making it, and therefore the limitation "wherein the at least one progestagens and the at least one estrogen are dissolved in the oil phase prior to being mixed with the aqueous phase"

amounts to a product-by-process limitation. Since the same product is obtained when the estradiol and progesterone are added to the formed emulsion as when they are added to the oil phase prior to forming the emulsion, the emulsion of the combined references meets the limitations of the claim.

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) MPEP 2113. See also In *SmithKline Beecham Corp. v. Apotex Corp.*, No. 04-1522 (Fed. Cir. February 24, 2006).

Furthermore, even if a different product is formed when the hormones are added to the oil phase prior to mixing with the aqueous phase, instead of adding the hormones to the formed emulsion, Simon teaches that the lipophilic drugs may be added to the oil phase separately prior to forming the emulsion (page 5, lines 23-27). Simon specifically teaches that lipophilic steroids are hydrophobic drugs that may be added to the oil phase, and cites progesterone as an example (page 5, lines 4-27); therefore, one skilled in the art would reasonably expect that estradiol, another lipophilic steroid, could also be added to the oil phase prior to mixing with the aqueous to form the emulsion. Additionally, adding progesterone and estradiol to the emulsion by dissolving them in the oil phase prior to being mixed with the aqueous phase is a conventional method for preparing two-phase emulsion systems, as taught by Heckenmuller et al (see rejection, above).

In response to applicant's arguments against the references individually (specifically, that Simon does not disclose an oil in water emulsion comprising at least

one progestagen and at least one estrogen, and Trotter teaches dissolving estradiol and progesterone in ethanol before mixing with Intralipid, pages 8-9 of Applicant's Remarks), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to Applicant's argument that estradiol is sparingly soluble in vegetable oils and therefore would be dissolved in the liposome phase of Simon, rather than the oil phase (page 9 of Applicant's Remarks), this argument is not persuasive because Simon also teaches that its compositions may be prepared "by a number of ways" (page 5, line 23), including adding the hydrophobic drug to the oily phase prior to forming the emulsion. Therefore, one skilled in the art would reasonably expect that the hydrophobic drug, even if only sparingly soluble in vegetable oil, could still be added to the oily phase prior to forming the emulsion. Additionally, even if the drug is only sparingly soluble in vegetable oil, Simon teaches that the oil of choice in its composition is not vegetable oil, but MCT oil, which has many advantages over vegetable oil, including enabling higher concentrations of the drug to be dissolved therein (page 3, line 55 - page 4, line 3). Therefore, one skilled in the art would reasonably expect hydrophobic drugs such as estradiol and progesterone, even if only sparingly soluble in vegetable oils, would still be able to be dissolved in the MCT oil, and thus could be formed by either method taught in Simon.

Claim Objections

11. Claims 2 and 3 are objected to because of the following informalities: the claims recite the phrase "at least one progestagens and at least one estrogen" (lines 3 and 8 of claim 2 and lines 2-3 of claim 3). It appears that the term "progestagens" should read "progestagen". Appropriate correction is required.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BARBARA FRAZIER whose telephone number is (571)270-3496. The examiner can normally be reached on Monday-Thursday 9am-4pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on (571)272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BSF

/Ashwin Mehta/
Primary Examiner, Technology Center 1600